

CLAIMS

What is claimed is:

5 1. A method of determining how the solubility of a solid compound-of-interest is affected by its form during a period between the early-lead optimization and clinical trials, which comprises:

10 (a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the form of the compound-of-interest in at least two of the samples is different;

15 (b) forming a liquid portion of each sample by adding a solvent to each sample; and

20 (c) determining how much compound-of-interest dissolved in the liquid portion of each sample.

15 2. The method of claim 1, wherein:

20 (a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;

25 (b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred;

30 (c) the physical form of the compound-of-interest in one sample differs from the physical form of the compound-of-interest in another sample;

35 (d) the compound-of-interest in one sample is amorphous and the compound-of-interest in another sample is crystalline;

40 (e) the compound-of-interest in one sample is crystalline and has a first crystal structure and/or a first crystal habit and the compound-of-interest in another sample is crystalline and has a second crystal structure and/or a second crystal habit, wherein the second crystal structure differs from the first crystal structure and/or the second crystal habit differs from the first crystal habit;

45 (f) the chemical form of the compound-of-interest in one sample differs from the chemical form of the compound-of-interest in another sample;

(g) the compound-of-interest in one sample is a salt, solvate, or co-crystal of a compound and the compound-of-interest in another sample is a different salt, solvate, or co-crystal of the compound;

5 (h) the compound-of-interest in one sample is a compound and the compound-of-interest in another sample is a salt, solvate, or co-crystal of the compound;

(i) the amount of compound-of-interest is less than about 100 micrograms;

(j) the amount of compound-of-interest is less than about 50 micrograms; or

(k) the amount of compound-of-interest is less than about 10 micrograms.

10 3. A method of determining how the dissolution of a solid compound-of-interest is affected by its form, which comprises:

(a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the form of the compound-of-interest in at least two of the samples is different;

15 (b) forming a liquid portion of each sample by adding a solvent to each sample; and

(c) determining how much compound-of-interest dissolved in the liquid portion of each sample as a function of time.

20 4. The method of claim 3, wherein:

(a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;

(b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred; or

25 (c) the method further comprises:

(i) preparing a first sub-array of samples, each comprising a controlled amount of the compound-of-interest in a first form;

(ii) preparing a second sub-array of samples, each comprising a controlled amount of the compound-of-interest in a second form that differs from the first form;

30 (iii) forming a liquid portion of each sample in the first sub-array by adding a controlled amount of a solvent to each sample in the first

sub-array at a time point that is unique to each sample in the first sub-array;

5 (iv) forming a liquid portion of each sample in the second sub-array by adding a controlled amount of a solvent to each sample in the second sub-array at a time point that is unique to each sample in the second sub-array but is the same as the time point at which solvent was added to a sample in the first sub-array;

10 (v) separating the liquid portion of each sample in the first and second sub-arrays from any solid portion each sample may contain at a time point that is the same for each sample in the first and second sub-arrays; and

(vi) determining how much compound-of-interest dissolved in the liquid portion of each sample;

(d) the physical form of the compound-of-interest in one sample differs from the physical form of the compound-of-interest in another sample;

15 (e) the compound-of-interest in one sample is amorphous and the compound-of-interest in another sample is crystalline;

(f) the compound-of-interest in one sample is crystalline and has a first crystal structure and/or a first crystal habit and the compound-of-interest in another sample is crystalline and has a second crystal structure and/or a second crystal habit, wherein the second crystal structure differs from the first crystal structure and/or the second crystal habit differs from the first crystal habit;

20 (g) the chemical form of the compound-of-interest in one sample differs from the chemical form of the compound-of-interest in another sample;

(h) the compound-of-interest in one sample is a salt, solvate, or co-crystal of a compound and the compound-of-interest in another sample is a different salt, solvate, or co-crystal of the compound;

25 (i) the compound-of-interest in one sample is a compound and the compound-of-interest in another sample is a salt, solvate, or co-crystal of the compound;

(j) the amount of compound-of-interest is less than about 100 micrograms;

30 (k) the amount of compound-of-interest is less than about 50 micrograms; or

(l) the amount of compound-of-interest is less than about 10 micrograms.

4. A method of determining how the stability of a solid compound-of-interest is affected by its form, which comprises:

5 (a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the form of the compound-of-interest in at least two of the samples is different;

(b) exposing the compound-of-interest in each sample to a condition that may affect the stability of the compound-of-interest; and

10 (c) determining whether the form or chemical composition of the compound-of-interest in each sample changed.

5. The method of claim 4 wherein:

15 (a) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, temperature, or time;

(b) the physical form of the compound-of-interest in one sample differs from the physical form of the compound-of-interest in another sample;

20 (c) the compound-of-interest in one sample is amorphous and the compound-of-interest in another sample is crystalline;

(d) the compound-of-interest in one sample is crystalline and has a first crystal structure and/or a first crystal habit and the compound-of-interest in another sample is crystalline and has a second crystal structure and/or a second crystal habit, wherein the second crystal structure differs from the first crystal structure and/or the second crystal habit differs from the first crystal habit;

25 (e) the chemical form of the compound-of-interest in one sample differs from the chemical form of the compound-of-interest in another sample;

30 (f) the compound-of-interest in one sample is a salt, solvate, or co-crystal of a compound and the compound-of-interest in another sample is a different salt, solvate, or co-crystal of the compound;

(g) the compound-of-interest in one sample is a compound and the compound-of-interest in another sample is a salt, solvate, or co-crystal of the compound;

5 (h) the amount of compound-of-interest is less than about 100 micrograms;

(i) the amount of compound-of-interest is less than about 50 micrograms; or

(j) the amount of compound-of-interest is less than about 10 micrograms.

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6. A method of determining how the hygroscopicity of a solid compound-of-interest is affected by its form, which comprises:

15 (a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the form of the compound-of-interest in at least two of the samples is different;

(b) exposing the compound-of-interest in each sample to a controlled relative humidity for a period of time; and

(c) determining the change in water content of the compound-of-interest in each sample.

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7. The method of claim 6 wherein:

25 (a) the physical form of the compound-of-interest in one sample differs from the physical form of the compound-of-interest in another sample;

(b) the compound-of-interest in one sample is amorphous and the compound-of-interest in another sample is crystalline;

(c) the compound-of-interest in one sample is crystalline and has a first crystal structure and/or a first crystal habit and the compound-of-interest in another sample is crystalline and has a second crystal structure and/or a second crystal habit, wherein the second crystal structure differs from the first crystal structure and/or the second crystal habit differs from the first crystal habit;

- (d) the chemical form of the compound-of-interest in one sample differs from the chemical form of the compound-of-interest in another sample;
- 5 (e) the compound-of-interest in one sample is a salt, solvate, or co-crystal of a compound and the compound-of-interest in another sample is a different salt, solvate, or co-crystal of the compound;
- (f) the compound-of-interest in one sample is a compound and the compound-of-interest in another sample is a salt, solvate, or co-crystal of the compound;
- 10 (g) the amount of compound-of-interest is less than about 100 micrograms;
- (h) the amount of compound-of-interest is less than about 50 micrograms; or

the amount of compound-of-interest is less than about 10 micrograms.

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8. A method of determining the effect of a condition on the solubility of a compound-of-interest, which comprises:

- (a) preparing an array of samples having a liquid portion, each comprising a controlled amount of the compound-of-interest and a solvent;
- 20 (b) exposing each sample to a condition that differs for at least two samples in the array; and
- (c) determining how much compound-of-interest dissolved in the liquid portion of each sample.

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9. The method of claim 8, wherein:

- (a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;
- 30 (b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred;

- (c) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, temperature, or time;
- (d) the amount of compound-of-interest is less than about 100 micrograms;
- 5 (e) the amount of compound-of-interest is less than about 50 micrograms; or
- (f) the amount of compound-of-interest is less than 10 micrograms.

10 10. A method of determining the effect of a condition on the dissolution of a compound-of-interest, which comprises:
(a) preparing an array of samples having a liquid portion, each comprising a controlled amount of the compound-of-interest and a solvent;
(b) exposing each sample to a condition that differs for at least two samples in the
15 array; and
(c) determining how much compound-of-interest dissolved in the liquid portion of each sample as a function of time.

11. The method of claim 10, wherein:

20 (a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;

(b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form
25 occurred;

(c) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, or temperature;

(d) the method further comprises:
30 (i) preparing a first sub-array of samples, each comprising a controlled amount of the compound-of-interest;

(ii) preparing a second sub-array of samples, each comprising a controlled amount of the compound-of-interest;

(iii) forming a liquid portion of each sample in the first sub-array by adding a solvent to each sample in the first sub-array at a time point that is unique to each sample in the first sub-array;

(iv) exposing each sample in the first sub-array to a first condition;

(v) forming a liquid portion of each sample in the second sub-array by adding a solvent to each sample in the second sub-array at a time point that is unique to each sample in the second sub-array but is the same as the time point at which solvent was added to a sample in the first sub-array;

(vi) exposing each sample in the second sub-array to a second condition that differs from the first condition;

(vii) separating the liquid portion of each sample in the first and second sub-arrays from any solid portion each sample may contain at a time point that is the same for each sample in the first and second sub-arrays; and

(viii) determining how much compound-of-interest dissolved in the liquid portion of each sample;

(e) the amount of compound-of-interest is less than about 100 micrograms;

(f) the amount of compound-of-interest is less than about 50 micrograms; or

(g) the amount of compound-of-interest is less than 10 micrograms.

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12. A method of determining the effect of a condition on the stability of a compound-of-interest, which comprises:

(a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the controlled amount is less than about 100 μ g;

(b) exposing each sample to a condition that differs for at least two samples in the array; and

(c) determining whether the form or chemical composition of the compound-of-interest in each sample changed.

13. The method of claim 12, wherein:

5 (a) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, temperature, or time;

(b) the amount of compound-of-interest is less than about 100 micrograms;

10 (c) the amount of compound-of-interest is less than about 50 micrograms; or

(d) the amount of compound-of-interest is less than 10 micrograms.

14. A method of determining the effect of a condition on the hygroscopicity 15 of a compound-of-interest, which comprises:

(a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest;

(b) exposing the compound-of-interest in each sample to a controlled relative humidity for a period of time and to an additional condition that differs for at least two 20 samples in the array; and

(c) determining the change in water content of the compound-of-interest in each sample.

15. The method of claim 14, wherein:

25 (e) the condition is pH, ionic strength, counter-ion concentration, radiation, oxidative conditions, mechanical stress, or temperature;

(f) the amount of compound-of-interest is less than about 100 micrograms;

(g) the amount of compound-of-interest is less than about 50 micrograms; or

30 (h) the amount of compound-of-interest is less than 10 micrograms.

16. A method of determining the effect of an excipient on the solubility of a compound-of-interest, which comprises:

(a) preparing an array of samples having a liquid portion, each comprising a controlled amount of the compound-of-interest, a solvent, and an excipient, wherein the excipient or the amount of excipient differs for at least two of the samples; and

5 (b) determining how much compound-of-interest dissolved in the liquid portion of each sample.

17. The method of claim 16, wherein:

10 (a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;

(b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred;

15 (c) the amount of excipient in at least one sample is zero;

(d) the excipient is a diluent, binder, lubricant, stabilizing or neutralizing agent, packaging reagent, or processing reagent;

(e) the amount of compound-of-interest is less than about 100 micrograms;

20 (f) the amount of compound-of-interest is less than 50 micrograms; or

(g) the amount of compound-of-interest is less than 10 micrograms.

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18. A method of determining the effect of an excipient on the dissolution of a compound-of-interest, which comprises:

(a) preparing an array of samples having a liquid portion, each comprising a controlled amount of the compound-of-interest, a solvent, and an excipient, wherein the excipient or the amount of excipient differs for at least two of the samples; and

30 (b) determining how much compound-of-interest dissolved in the liquid portion of each sample as a function of time.

19. The method of claim 18, wherein

- (a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;
- (b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred; or
- (c) the method further comprising:
 - (i) preparing a first sub-array of samples, each comprising a controlled amount of the compound-of-interest and a first excipient;
 - (ii) preparing a second sub-array of samples, each comprising a controlled amount of the compound-of-interest and a second excipient that differs from the first excipient and/or is provided in a different amount than the first excipient;
 - (iii) forming a liquid portion of each sample in the first sub-array by adding a solvent to each sample in the first sub-array at a time point that is unique to each sample in the first sub-array;
 - (iv) forming a liquid portion of each sample in the second sub-array by adding a solvent to each sample in the second sub-array at a time point that is unique to each sample in the second sub-array but is the same as the time point at which solvent was added to a sample in the first sub-array;
 - (v) separating the liquid portion of each sample in the first and second sub-arrays from any solid portion each sample may contain at a time point that is the same for each sample in the first and second sub-arrays; and
 - (vi) determining how much compound-of-interest dissolved in the liquid portion of each sample;
- (d) the amount of excipient in at least one sample is zero;
- (e) the excipient is a diluent, binder, lubricant, stabilizing or neutralizing agent, packaging reagent, or processing reagent;
- (f) the amount of compound-of-interest is less than about 100 micrograms;

- (g) the amount of compound-of-interest is less than 50 micrograms; or

- (h) the amount of compound-of-interest is less than 10 micrograms.

20. A method of determining the effect of an excipient on the stability of a compound-of-interest, which comprises:

- 5 (a) preparing an array of samples, each of which comprises a controlled amount of the compound-of-interest and an excipient, wherein the excipient or the amount of excipient differs for at least two of the samples;
- 10 (b) exposing the samples to a condition that may affect the stability of the compound-of-interest; and
- (c) determining whether the form or chemical composition of the compound-of-interest in each sample changed.

21. The method of claim 20, wherein:

- 15 (a) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, temperature, or time;
- (b) the amount of excipient in at least one sample is zero;
- (c) the excipient is a diluent, binder, lubricant, stabilizing or neutralizing agent, packaging reagent, or processing reagent;
- 20 (d) the amount of compound-of-interest is less than about 100 micrograms;
- (e) the amount of compound-of-interest is less than 50 micrograms; or
- (f) the amount of compound-of-interest is less than 10 micrograms.

25 22. A method of determining the effect of an excipient on the hygroscopicity of a compound-of-interest, which comprises:

- (a) preparing an array of samples, each of which comprises a controlled amount of the compound-of-interest and an excipient, wherein the excipient or the amount of excipient differs for at least two of the samples;
- 30 (b) exposing the samples to a controlled relative humidity for a period of time; and

(c) determining the change in water content of the compound-of-interest in each sample.

23. The method of claim 22, wherein:

- 5 (g) the amount of excipient in at least one sample is zero;
- (h) the excipient is a diluent, binder, lubricant, stabilizing or neutralizing agent, packaging reagent, or processing reagent;
- (i) the amount of compound-of-interest is less than about 100 micrograms;
- 10 (j) the amount of compound-of-interest is less than 50 micrograms; or
- (k) the amount of compound-of-interest is less than 10 micrograms.